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# Preoperative Weight Loss With GLP-1 Receptor Agonist Treatment Predicts Greater Weight Loss Achieved by the Combination of Medical Weight Management And Bariatric Surgery In Patients With Type 2 Diabetes: A Longitudinal Analysis

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## Abstract

We examined the relationship between weight changes following preoperative glucagon-like peptide-1 receptor agonist (GLP-1 RA) and weight changes from the start of medical weight management (MWM) till 12 months after bariatric surgery in patients with Type 2 diabetes in a retrospective cohort study. Forty-five patients (64.4% women, median age 49 (IQR 45-60) years) were included. The median weight loss from start of MWM until 12 months post-surgery was 17.9% (13.0%-29.3%). GLP-1 RA during MWM resulted in 5.0% (1.9%-7.7%) weight loss. Weight loss during GLP-1 RA treatment predicted weight loss from the start of MWM till 12 months post-surgery; but not post-operative weight loss following adjustment. The proportion of weight loss from start of MWM to 12 months post-surgery attributed to GLP-1 RA was negatively associated with that attributed to surgery following adjustment. In conclusion, weight change following GLP-1 RA predicted the weight loss achieved by a combination of MWM and bariatric surgery, but not weight loss induced by surgery only. Failure to lose weight following GLP-1 RA should not be considered a barrier to having bariatric surgery.

Keywords: Bariatric Surgery; GLP-1 RA; Glucagon-like peptide-1 receptor agonist; LAGB; Laparoscopic Adjustable Gastric Band; LSG; Laparoscopic Sleeve Gastrectomy; Obesity; Roux-en-Y Gastric Bypass; RYGB; T2DM; Type 2 Diabetes Mellitus; Weight Loss.

## Introduction

Whether weight loss prior to bariatric surgery can improve the overall weight loss from the start of medical weight management (MWM) to post-bariatric surgery is unknown. In addition, due to the variation in post-surgical weight loss, there is much interest in identifying pre-operative predictors of post-surgical weight loss<sup>1,2</sup>

Gut hormones, such as peptide YY (PYY) and glucagon-like peptide 1 (GLP-1), play an important role in the weight loss observed after Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (LSG).<sup>3-6</sup>

We hypothesised that greater weight change achieved by GLP-1 receptor agonist (GLP-1 RA) treatment before surgery predicts greater post-surgical weight loss and greater weight loss from the start of MWM to 12 months post-surgery. The observation that the amount of weight loss within 16 weeks of starting GLP-1 RA predicts weight loss at 1 year of treatment with GLP-1 RA further supports that the initial response to GLP-1 RA may be a good predictor of long term weight loss.<sup>7</sup>

In this study, our primary aim was to assess the relationship between preoperative GLP-1 RA induced weight changes and the weight change achieved from the start of MWM till 12 months post-bariatric surgery (Total weight change TWC). A secondary aim was to assess the relationship between weight changes following preoperative GLP-1 RA treatment and surgically-induced weight changes at 12 months after bariatric surgery. For more detailed background please refer to the online supplement.

## Methods

We conducted a retrospective cohort study of patients with Type 2 diabetes mellitus (T2DM) who attended Tier 3 MWM, received GLP-1 RA treatment preoperatively, underwent bariatric surgery and were followed-up for 12 months post-surgery at a single tertiary centre in the UK.

For full methods, and ethical considerations, please refer to the online supplement.

## Results

Forty-five patients were included in this analysis (26 gastric band, 16 RYGB and 3 LSG). The study population was mostly composed of middle age women with grade III obesity (Table S1). Liraglutide once-daily was used in 35 patients, while 10 patients received Exenatide twice-daily. Eight patients received GLP-1 RA treatment post-operatively to improve glycaemic control at the discretion of the treating physician.

GLP-1 RA and bariatric surgery resulted in significant weight loss (**Table S2**). Please refer to the online supplement for details

### The relationships between pre- and post-operative weight changes

There was no relationship between GLP-1 RA induced weight change and the weight change induced by bariatric surgery over 12 months, regardless of the type of the surgical procedure (**Tables S3 and S4**). Using multiple linear regression, greater % weight loss before starting GLP-1 RA predicted lower % weight loss after bariatric surgery after adjustment (please refer to the online supplement).

### The relationship between GLP-1 RA-induced weight changes and TWC from start of MWM till 12 months post-surgery

Greater weight loss after initiating GLP-1 RA was associated with greater weight loss from the start of MWM to 12 months post-surgery (**Table 1**).

Using multiple linear regression, and after adjusting for % weight change from baseline to the start of GLP-1 RA, the % weight change induced by GLP-1 RA, the % weight change induced by surgery by 12 months, baseline weight in kg, gender, age and type of surgery (for the model:  $R = 0.98$ ,  $R^2 = 0.97$ ); % weight change before starting GLP-1 RA ( $B = 0.6$ ,  $p < 0.001$ ), during GLP-1 RA ( $B = 0.7$ ,  $p < 0.001$ ) and 12 months following surgery ( $B = 0.9$ ,  $p < 0.001$ ) predicted the TWC from the start of medical WM to 12 months post-surgery. This suggests that greater TWC was predicted by either a greater pre- or a post-bariatric surgery weight loss.

## The relationships between pre- and post- operative weight changes as proportions of the TWC from the start of MWM to 12 months after bariatric surgery

The greater % of total weight loss achieved either before or after GLP-1 RA, the lesser the contribution of surgically induced weight loss to the total weight loss achieved from the start of the MWM to 12 months post-operatively regardless of surgical procedure (**Table 2**).

Using linear regression and after adjusting for age, sex, surgical procedure, the proportion of TWC attributed to GLP-1 RA and the proportion of the TWC attributed to before GLP-1 RA (for the model:  $R=0.912$ ,  $R^2=0.832$ ); the proportion of TWC due to bariatric surgery was predicted by the proportion of TWC before ( $B=-0.992$ ,  $p=0.002$ ) and after GLP-1 RA ( $B=-0.854$ ,  $p<0.001$ ). This suggests that the greater the proportion of total weight loss achieved before GLP-1 RA or after GLP-1 RA, the less the contribution of bariatric surgery to the total weight loss.

## Discussion

This is the first analysis that examined the relationship between preoperative GLP-1 RA treatment and the weight loss achieved from the start of MWM till 12 months post-bariatric surgery and the surgically-induced weight loss. Our results showed that weight loss achieved in MWM before or after GLP-1 RA treatment predicted greater TWC. However, the contribution of bariatric surgery to TWC was less in those who lost more weight following GLP-1 RA treatment preoperatively. In addition, we have shown that the impact of GLP-1 RA treatment before bariatric surgery does not predict the weight loss achieved following bariatric surgery. There was no difference in post-bariatric surgery weight loss in those who lost weight following GLP-1 RA treatment and those who did not lose weight.

There may be several explanations for the lack of relationship between weight changes following GLP-1 RA and post bariatric surgery. One possible explanation is that post-operative weight loss is multifactorial and not only dependent on GLP-1. Hence, response to GLP-1 treatment on its own

may not be able to predict post-surgical weight loss.<sup>8</sup> Another plausibility is that GLP-1 levels differ following bariatric surgery and GLP-1 RA as bariatric surgery produces higher portal levels of GLP-1 while GLP-1 RA are administered peripherally and not directly into the portal system.<sup>8</sup> In addition, recent evidence is suggestive that the breakdown products of GLP-1 degradation by DPP-4 might not be as metabolically inactive as has been believed before<sup>9</sup>. Hence, the increased GLP-1 secretion following bariatric surgery might have different metabolic effects compared to the GLP-1 RA treatment.<sup>8</sup> Furthermore, recent rodent studies started to cast a doubt about the role of GLP-1 following RYGB or LSG<sup>10,11</sup> but data collected from humans suggest a central role for GLP-1 in the weight loss after bariatric surgery.<sup>12</sup> One animal study showed that the response to GLP-1 RA, exendin-4, predicted some of the metabolic impacts of post-RYGB, particularly in relation to glucose levels but data from humans are lacking.<sup>13</sup>

We found that greater weight loss before or after starting GLP-1 RA was associated with greater TWC achieved from the start of MWM to 12 months post-bariatric surgery. Conversely, our results also showed that the greater the proportion of weight loss achieved by pharmacological or non-pharmacological interventions before surgery then the less contribution of bariatric surgery to the TWC from start of MWM to 12 months post-surgery. A previous study also found weight loss before RYGB led to slightly less weight loss 12 months after surgery compared to patients who did not demonstrate any preoperative weight loss.<sup>14</sup> Taken together, these findings suggest that the amount of weight loss that can be achieved in any individual may be predetermined by several biological factors (a weight set-point),<sup>15</sup> and losing weight before surgery reduces the contribution of surgery to the total weight loss but surgery will still result in significant weight loss regardless of the response (or lack of) to pharmacological or non-pharmacological interventions before surgery. However, there is a wide variation in individuals' weight set-points and their potential to lose weight, and while the contribution of bariatric surgery to the total weight loss might be less in patients who lost weight before surgery, the ability of an individual to lose weight (if calculated from start of MWM) can be predicted by their pre-operative GLP-1 RA-induced weight loss.

The implications are that patients receiving GLP-1 RA should be counselled that although the absolute weight loss after a combined strategy will be more in those that respond to GLP-1 RA, the relative contribution of the surgical component may be less. Thus, this is not a failure of surgery but rather an illustration of how medical and surgical therapy can shift an individual's weight set point and that those patients that can lose more weight initially with non-surgical interventions are also the ones that can lose most weight overall following bariatric surgery.

Our data also suggest that when assessing the impact of bariatric surgery on weight, the weight loss in the periods preceding surgery needs to take into account, and that variation in post-surgical weight loss might reflect variation in pre-operative pharmacologically and non-pharmacologically-induced weight loss.

In addition, our findings also suggest that there is a need to individualise treatment approaches to patients with obesity. It seems that some patients may not lose much weight with lifestyle interventions or pharmacotherapy, but will still greatly benefit from bariatric surgery. In these individuals, bariatric surgery should not be delayed as it is the main mode of treatment. In other individuals who respond well to life style interventions or pharmacotherapy, bariatric surgery will still aid further weight loss and the preoperative weight loss in these individuals seems to predict greater overall weight loss; and in these individual's bariatric surgery will still counteract the usual metabolic adaptations that occur following non-surgical weight loss.<sup>16</sup>

Our study has several limitations and strengths, please refer to the online supplement for full details.

In conclusion, weight change induced by preoperative GLP-1 RA correlated with the TWC induced by a strategy of GLP-1 RA followed by bariatric surgery. GLP-1 RA induced weight loss did not predict the weight loss induced by only the surgical component of the strategy, but bariatric surgery on its own still induced significant weight loss. This suggests the presence of an individualised weight loss set-point that can be reached using multiple interventions, but which is hard to exceed. The implications are that patients receiving GLP-1 RA should be counselled that although the absolute



weight loss after a combined strategy will lead to greater weight loss in those that respond to GLP-1 RA, the relative contribution of the surgical component may be less. Thus, this is not a failure of surgery; but rather an illustration of how medical and surgical therapy can shift an individual's weight set point and that those patients that can lose more weight initially with non-surgical interventions are also the ones that can lose most weight overall.

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*Table 1: The correlations between GLP-1 RA induced weight change and total weight change (TWC) calculated from start of medical weight management to 12 months post bariatric surgery*

	r value	p-value
<b>Total Study Population (n=45)</b>		
Correlations between GLP-1 RA induced weight change in Kg, and TWC in Kg	0.31	0.04
Correlations between GLP-1 RA induced weight change in %, and Percentage TWC	0.26	0.08
<b>LAGB (n= 26)</b>		
Correlations between GLP-1 RA induced weight change in Kg, and TWC in Kg	0.42	0.03
Correlations between GLP-1 RA induced weight change in %, and Percentage TWC	0.40	0.045
<b>RYGB/LSG (n= 19)</b>		
Correlations between GLP-1 RA induced weight change in Kg, and TWC in Kg	0.46	0.05
Correlations between GLP-1 RA induced weight change in %, and Percentage TWC	0.40	0.09

*Table 2. Correlations between weight change before GLP-1 RA, after GLP-1 and after surgery presented as proportion of Total Weight Change (TWC). LAGB: Laparoscopic Adjustable Gastric Band; RYGB: Roux-en-Y Gastric Bypass; LSG: Laparoscopic Sleeve Gastrectomy; GLP-1 RA: Glucagon-like peptide-1 receptor agonist.*

	Correlations with	r value	p-value
<b>Total Study Population (n= 45)</b>			
% of total weight change attributed to weight change before GLP-1 RA treatment	% of total weight change attributed to GLP-1 RA treatment	-0.274	0.069
	% of total weight change attributed to surgery	-0.457	0.002
% of total weight change attributed to GLP-1 RA treatment	% of total weight change attributed to surgery	-0.407	0.006
<b>LAGB (n= 26)</b>			
% of total weight change attributed to weight change before GLP-1 RA treatment	% of total weight change attributed to GLP-1 RA treatment	-0.309	0.125
	% of total weight change attributed to surgery	-0.359	0.072
% of total weight change attributed to GLP-1 RA treatment	% of total weight change attributed to surgery	-0.448	0.022
<b>RYGB/ LSG (n= 19)</b>			
% of total weight change attributed to weight change before GLP-1 RA treatment	% of total weight change attributed to GLP-1 RA treatment	-0.065	0.791
	% of total weight change attributed to surgery	-0.576	0.010
% of total weight change attributed to GLP-1 RA treatment	% of total weight change attributed to surgery	-0.535	0.018